Adefovir dipivoxil

Brand Name: Hepsera
Drug Class: Opportunistic Infection and Other Drugs

Drug Description

Adefovir is an acyclic nucleotide analogue of adenosine monophosphate with activity against hepatitis B virus (HBV). Adefovir dipivoxil is the diester prodrug of adefovir. [1]

HIV/AIDS-Related Uses

Adefovir dipivoxil was at one time being developed for the treatment of HIV disease, achieving anti-HIV activity at a substantially higher dose than that used to treat HBV. However, nephrotoxicity was a treatment-limiting toxicity of adefovir dipivoxil therapy at the higher dose required for HIV therapy.[2] In December 1999, Gilead Sciences announced the termination of its adefovir dipivoxil development program for the treatment of HIV.[3]

Non-HIV/AIDS-Related Uses

The FDA approved adefovir dipivoxil on September 20, 2002, for the treatment of chronic HBV infection in adults with evidence of active viral replication and evidence of either persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.[4] Efficacy and safety have also been evaluated in patients with lamivudine-resistant virus and in pre- and post-liver transplant patients.[5]

Pharmacology

Adefovir dipivoxil is the diester prodrug of adefovir and is rapidly converted by diester hydrolysis after oral administration.[6] Adefovir is phosphorylated to the active metabolite, adefovir diphosphate, by cellular kinases. Adefovir diphosphate, a nucleotide analogue, inhibits HBV polymerase by competing with the natural substrate deoxyadenosine triphosphate and by causing DNA chain termination after its incorporation into viral DNA.[7] The approximate oral bioavailability of adefovir from a single 10 mg dose of adefovir dipivoxil is 59%. Following oral administration of a single dose of adefovir dipivoxil 10 mg, the median peak adefovir plasma concentration (Cmax) was 18.4 ng/ml and occurred at a median 1.75 hours postdose. Terminal elimination half-life of plasma adefovir is approximately 7.48 hours.[8]

In vitro binding of adefovir to human plasma or human serum proteins is less than or equal to 4% over the adefovir concentration range of 0.1 to 25 mcg/ml. The volume of distribution at steady state is approximately 392 and 352 ml/kg following IV administration of 1.0 or 3.0 mg/kg/day, respectively.[9]

Adefovir is renally excreted by a combination of glomerular filtration and active tubular secretion; 45% of a dose is recovered in the urine over 24 hours. Thirty-five percent of a dose is removed during four-hour hemodialysis.[10]

Cmax, area under the plasma concentration-time curve (AUC), and half-life are increased in patients with moderately or severely impaired renal function or with end-stage renal disease requiring hemodialysis compared to people with normal renal function. It is recommended that the dosing interval be modified in patients with renal impairment.[11]

Adefovir dipivoxil is in FDA Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. Studies in rats and rabbits at doses 23 to 40 times greater than human exposure, respectively, identified no embryotoxicity or teratogenicity.[12] To monitor fetal outcomes of pregnant women exposed to adefovir dipivoxil, an Antiretroviral Pregnancy Registry has been established. Health care providers are encouraged to register patients online at http://www.APRegistry.com or by calling 1-800-258-4263. It is not known whether adefovir is excreted in human milk; breastfeeding is discouraged in women taking adefovir dipivoxil.[13]

There are no data on the effect of adefovir on HBV transmission from mothers to infants. Infant immunization should be used to prevent neonatal HBV infection. The safety and efficacy of adefovir dipivoxil has not been established in the pediatric population.[14]

N236T and A181V mutations have been identified in genotypic analyses as contributors to adefovir

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Pharmacology (cont.)

resistance. Both mutations have caused a decrease in lamivudine susceptibility in vitro. Recombinant HBV variants containing mutations associated with lamivudine resistance (L180M, M204V, V173L) in the HBV polymerase gene were susceptible to adefovir in vitro. HBV variants with polymerase mutations R or W501Q, both associated with resistance to HBV immunoglobulin, and T128N were susceptible to adefovir in vitro.[15]

Adefovir has activity against HIV but only at much higher doses than those used to treat HBV. A chronic HBV patient with unrecognized or untreated HIV infection may develop HIV resistance to adefovir when taken at HBV-approved, non-HIV-suppressive doses. Although adefovir has not been shown to suppress HIV RNA in patients, limited data are available on the use of adefovir to treat patients coinfected with HBV and HIV.[16] [17]

A randomized, double-blind, placebo-controlled trial compared daily tenofovir DF 300 mg to adefovir dipivoxil 10 mg therapy in 52 HIV/HBV coinfected patients on stable HAART. At baseline, 75% of patients had HIV RNA levels below 50 copies/ml and 98% had compensated liver disease. During monthly evaluations over 48 weeks, both drugs successfully lowered HBV DNA levels and were considered safe and effective in HIV/HBV coinfected patients.[18]

Adverse Events/Toxicity

Severe acute exacerbation of hepatitis, rarely but potentially fatal, has been reported in patients who discontinue anti-HBV therapy with adefovir dipivoxil. Patients should be monitored for hepatic dysfunction at repeated intervals over a period of time; resumption of adefovir dipivoxil treatment may be warranted.[19]

Nephrotoxicity, characterized by a delayed onset of gradual increases in serum creatinine and decreases in serum phosphorus, is the primary dose-limiting toxicity of adefovir dipivoxil therapy at the substantially higher doses required for HIV antiviral activity. This toxicity is also possible at the lower dose required for HBV antiviral activity when given to chronic HBV patients long-term.[20]

Lactic acidosis and severe hepatomegaly with steatosis, potentially fatal, have been reported with the use of nucleoside analogues alone or in combination with other antiretrovirals. Female gender, obesity, and prolonged nucleoside analogue exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogues to any patient with known risk factors for liver disease; however, cases of hepatotoxicity have also been reported in patients with no known risk factors. Treatment with adefovir dipivoxil should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity, which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations.[21]

Severe adverse effects possible with adefovir treatment include hematuria and glycosuria. Moderate adverse effects that have been reported in patients taking adefovir dipivoxil include asthenia, abdominal pain, headache, and more rarely, diarrhea, dyspepsia, flatulence, heartburn, and nausea.[22]

Pre- and post-liver transplantation patients with chronic HBV and clinical evidence of lamivudine resistance and patients with underlying renal insufficiency or other risk factors for renal dysfunction represent special risk groups. Common treatment-related adverse events reported in these patients include hepatic failure, increases in ALT and AST, abnormal liver function, increased coughing, pharyngitis, sinusitis, pruritus, rash, increases in serum creatinine, renal failure, and renal insufficiency.[23]

Drug and Food Interactions

Adefovir dipivoxil may be taken without regard to food.[24]

Because adefovir is eliminated by the kidney, coadministration of adefovir dipivoxil with renally excreted drugs or nephrotoxic drugs may cause further nephrotoxicity or may increase serum concentrations of either adefovir or the coadministered drugs. Patients should be monitored closely for adverse events when adefovir dipivoxil

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Drug and Food Interactions (cont.)

is coadministered with drugs that are excreted renally or are known to affect renal function, such as aminoglycosides, cyclosporin, and nonsteroidal anti-inflammatory drugs. Adefovir does not appear to interact with concurrently administered lamivudine, acetaminophen, or sulfamethoxazole/trimethoprim.[25]

When adefovir dipivoxil was coadministered with ibuprofen 800 mg three times daily, adefovir Cmax and AUC increased by 33% and 23%, respectively. The clinical significance of this increase in adefovir exposure is unknown.[26]

Adefovir does not inhibit or act as a substrate for cytochrome P450 (CYP450) enzymes. The potential for adefovir to induce CYP450 enzymes is not known. Based on the results of in vitro experiments and the renal elimination pathway of adefovir, the potential for CYP450-mediated interactions between adefovir and other medicines is low.[27]

Administration of adefovir dipivoxil with nucleoside analogues increases the risk of lactic acidosis and severe hepatomegaly with steatosis. Coadministration of these drugs should be suspended in patients who develop symptoms or laboratory findings indicative of hepatic toxicity.[28]

Contraindications

Adefovir is contraindicated in patients with hypersensitivity to adefovir or any components of the formulation.[29]

Clinical Trials

For information on clinical trials that involve Adefovir dipivoxil, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Adefovir dipivoxil AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[30]

Dosage Form: Tablets containing adefovir dipivoxil 10 mg.[31]

Once-daily dosing is recommended by the manufacturer for patients with normal renal function. The manufacturer suggests the following altered dosage regimens for patients with renal impairment: 10 mg every other day for creatinine clearance (CrCl) of 20 to 49 ml/min, 10 mg every three days for CrCl of 10 to 19 ml/min, and 10 mg every 7 days after dialysis for patients receiving hemodialysis.[32]

Storage: Store in original container at 25 C (77 F), with excursions permitted at 15 C to 30 C (59 F to 86 F).[33]

Chemistry

CAS Name: Propanoic acid, 2,2-dimethyl-, ([(2-[6-amino-9H-purin-9-yl]ethoxy) methyl]phosphinylidene) bis(oxymethylene) ester[34]

CAS Number: 142340-99-6[35]

Molecular formula: C20-H32-N5-O8-P[36]

C47.90%, H6.43%, N13.97%, O25.52%, P6.18%[37]

Molecular weight: 501.47[38]

Melting point: Greater than 250 C[39]

Physical Description: Off-white crystalline powder.[40]

Solubility: Aqueous solubility of 19 mg/ml at pH 2 and 0.4 mg/ml at pH 7.2.[41]

Other Names

GS-840[42]

Preveon[43]

PMEA[44]

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Further Reading

Benhamou Y, Bonyhay L. Treatment of hepatitis B virus infection in patients coinfected with HIV. Gastroenterol Clin North Am. 2004 Sep;33(3):617-27. Review.

Danta M, Dusheiko G. Adefovir dipivoxil: review of a novel acyclic nucleoside analogue. Int J Clin Pract. 2004 Sep;58(9):877-86. Review.

Delaugerre C, Marcelin AG, Thibault V, Peytavin G, Bombled T, Bochet MV, Katlama C, Benhamou Y, Calvez V.Human immunodeficiency virus (HIV) Type 1 reverse transcriptase resistance mutations in hepatitis B virus (HBV)-HIV-coinfected patients treated for HBV chronic infection once daily with 10 milligrams of adefovir dipivoxil combined with lamivudine. Antimicrob Agents Chemother. 2002 May;46(5):1586-8.

Murphy MJ, Wilcox RD. Management of the coinfected patient: human immunodeficiency virus/hepatitis B and human immunodeficiency virus/hepatitis C. Am J Med Sci. 2004 Jul;328(1):26-36.

Thio CL. Management of chronic hepatitis B in the HIV-infected patient. AIDS Read. 2004 Mar;14(3):122-9, 133, 136-7. Review.

Manufacturer Information

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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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References

1. Gilead Sciences - Hepsera Prescribing Information, August 2004, p. 1. Available at: http://www.hepsera.com. Accessed 05/26/05.

2. Gilead Sciences - Hepsera Description. Available at: http://www.hepsera.com. Accessed 05/26/05.

3. Gilead Sciences - Gilead Sciences Announces Termination of Its U.S. Development Program for Adefovir Dipivoxil for HIV [Press Release, 12/03/99]. Available at: http://www.gilead.com/wt/sec/pr_944254502. Accessed 05/26/05.

4. USP DI - 2005; p. 37

5. Gilead Sciences - Hepsera Clinical Data. Available at: http://www.hepsera.com. Accessed 05/26/05.

6. AHFS Drug Information - 2005; p. 781

7. USP DI - 2005; p. 37

8. USP DI - 2005; p. 37

9. Gilead Sciences - Hepsera Prescribing Information, August 2004, p. 4. Available at: http://www.hepsera.com. Accessed 05/26/05.

10. USP DI - 2005; p. 37

11. USP DI - 2005; p. 37

12. USP DI - 2005; p. 38

13. AHFS Drug Information - 2005; p. 781

14. USP DI - 2005; p. 38

15. Gilead Sciences - Hepsera Prescribing Information, August 2004, pp. 2-3. Available at: http://www.hepsera.com. Accessed 05/26/05.

16. Gilead Sciences - Hepsera Prescribing Information, August 2004, p. 10. Available at: http://www.hepsera.com. Accessed 05/26/05.

17. AHFS Drug Information - 2005; pp. 780-1

18. Conf Retroviruses Opportunistic Infect. - 12th, 2005. Abstract 124.

19. AHFS Drug Information - 2005; pp. 780-1

20. AHFS Drug Information - 2005; pp. 780-1

21. USP DI - 2005; p. 38

22. USP DI - 2005; pp. 38-9

23. USP DI - 2005; p. 38

24. AHFS Drug Information - 2005; p. 780

25. AHFS Drug Information - 2005; p. 781

26. AHFS Drug Information - 2005; p. 781

27. USP DI - 2005; p. 38

28. USP DI - 2005; p. 38

29. AHFS Drug Information - 2005; p. 780

30. AHFS Drug Information - 2005; p. 780

31. AHFS Drug Information - 2005; p. 780

32. USP DI - 2005; p. 39

33. USP DI - 2005; p. 39

34. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 05/26/05.

35. Merck Index - 2001; p. 29

36. Merck Index - 2001; p. 29

37. Calculation. -

38. Merck Index - 2001; p. 29

39. Merck Index - 2001; p. 29

40. Merck Index - 2001; p. 29

41. USP DI - 2005; p. 37

42. Merck Index - 2001; p. 29

43. Merck Index - 2001; p. 29

44. Expert Rev Anti Infect Ther - 2003 Jun;1(1):21-43